CALCIPOTRIENE AND BETAMETHASONE DIPROPIONATE- calcipotriene and betamethasone dipropionate ointment
Prasco Laboratories

HIGHLIGHTS OF PRESCRIBING INFORMATION
These highlights do not include all the information needed to use Calcipotriene and Betamethasone Dipropionate Ointment safely and effectively. See Full Prescribing Information for Calcipotriene and Betamethasone Dipropionate Ointment.

Calcipotriene and Betamethasone Dipropionate Ointment, for topical use
Initial U.S. Approval: 2006

INDICATIONS AND USAGE

Calcipotriene and Betamethasone Dipropionate Ointment is a vitamin D analogue and corticosteroid combination product indicated for the topical treatment of plaque psoriasis in patients 12 years of age and older. (1)

DOSAGE AND ADMINISTRATION

- Apply Calcipotriene and Betamethasone Dipropionate Ointment to affected area(s) once daily for up to 4 weeks. Discontinue therapy when control is achieved. (2)
- Adult patients should not use more than 100 g per week. (2)
- Patients ages 12 to 17 years should not use more than 60 g per week. (2)
- Treatment of more than 30% body surface area is not recommended. (2)
- Do not use with occlusive dressings unless directed by a physician. (2)
- Avoid use on the face, groin, or axillae, or if skin atrophy is present at the treatment site. (2)
- Not for oral, ophthalmic, or intravaginal use. (2)

DOSAGE FORMS AND STRENGTHS

Ointment, 0.005%/0.064% (3)

CONTRAINDICATIONS

None. (4)

WARNINGS AND PRECAUTIONS

- Hypercalcemia and hypercalciuria have been observed. If either occurs, discontinue treatment until parameters of calcium metabolism normalize. (5.1)
- Calcipotriene and Betamethasone Dipropionate Ointment can produce reversible hypothalamic-pituitary-adrenal (HPA) axis suppression with the potential for glucocorticosteroid insufficiency during and after withdrawal of treatment. Risk factors include the use of high-potency topical corticosteroid, use over a large surface area or to areas under occlusion, prolonged use, concomitant use of more than one corticosteroid-containing product, altered skin barrier, liver failure, and use in pediatric patients. Modify use should HPA axis suppression develop. (5.2, 8.4)
- Calcipotriene and Betamethasone Dipropionate Ointment may increase the risk of cataract and glaucoma. If visual symptoms occur, consider referral to an ophthalmologist. (5.3)

ADVERSE REACTIONS

The most common adverse reactions (≥1%) are pruritus and scaly rash. (6.1)

To report SUSPECTED ADVERSE REACTIONS, contact LEO Pharma Inc. at 1-877-494-4536 or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.
See 17 for PATIENT COUNSELING INFORMATION and FDA-approved patient labeling.

Revised: 3/2020

FULL PRESCRIBING INFORMATION: CONTENTS*

* Sections or subsections omitted from the full prescribing information are not listed.

FULL PRESCRIBING INFORMATION

1 INDICATIONS AND USAGE

Calcipotriene and Betamethasone Dipropionate Ointment is indicated for the topical treatment of plaque psoriasis in patients 12 years of age and older.

2 DOSAGE AND ADMINISTRATION

Apply an adequate layer of Calcipotriene and Betamethasone Dipropionate Ointment to the affected area(s) once daily for up to 4 weeks. Calcipotriene and Betamethasone Dipropionate Ointment should be rubbed in gently and completely. Patients should wash their hands after applying Calcipotriene and Betamethasone Dipropionate Ointment. Therapy should be discontinued when control is achieved.

Patients 18 years and older should not use more than 100 g per week and patients 12 to 17 years should not use more than 60 g per week. Treatment of more than 30% body surface area is not recommended.

Calcipotriene and Betamethasone Dipropionate Ointment should not be used with occlusive dressings unless directed by a physician. Avoid use on the face, groin, or axillae, or if skin atrophy is present at the treatment site. Calcipotriene and Betamethasone Dipropionate Ointment is not for oral, ophthalmic,

or intravaginal use.

3 DOSAGE FORMS AND STRENGTHS

Ointment, 0.005%/0.064%

Each gram of Calcipotriene and Betamethasone Dipropionate Ointment contains 52.18 mcg of calcipotriene hydrate (equivalent to 50 mcg of calcipotriene) and 0.643 mg of betamethasone dipropionate (equivalent to 0.5 mg of betamethasone) in off-white to yellow paraffin ointment base.

4 CONTRAINDICATIONS

None.

5 WARNINGS AND PRECAUTIONS

5.1 Hypercalcemia and Hypercalciuria

Hypercalcemia and hypercalciuria have been observed with use of Calcipotriene and Betamethasone Dipropionate Ointment. If hypercalcemia or hypercalciuria develops, treatment should be discontinued until parameters of calcium metabolism have normalized. In the trials that included assessment of the effects of Calcipotriene and Betamethasone Dipropionate Ointment on calcium metabolism, such testing was done after 4 weeks of treatment. The effects of Calcipotriene and Betamethasone Dipropionate Ointment on calcium metabolism following treatment durations of longer than 4 weeks have not been evaluated *[see Clinical Pharmacology (12.2)]*.

5.2 Effects on Endocrine System

Calcipotriene and Betamethasone Dipropionate Ointment can cause reversible hypothalamic-pituitary-adrenal (HPA) axis suppression with the potential for clinical glucocorticosteroid insufficiency. This may occur during treatment or upon withdrawal of treatment. Factors that predispose a patient to HPA axis suppression include the use of high-potency corticosteroids, large treatment surface areas, prolonged use, concomitant use of more than one corticosteroid-containing product, use of occlusive dressings, altered skin barrier, liver failure, and young age. Evaluation for HPA axis suppression may be done by using the cosyntropin stimulation test *[see Clinical Pharmacology (12.2)]*.

In a trial evaluating the effects of Calcipotriene and Betamethasone Dipropionate Topical Suspension and Calcipotriene and Betamethasone Dipropionate Ointment on the HPA axis, 32 adult subjects were treated with Calcipotriene and Betamethasone Dipropionate Topical Suspension on the scalp and Calcipotriene and Betamethasone Dipropionate Ointment on the body. Adrenal suppression was identified in 5 of 32 subjects (15.6%) after 4 weeks of treatment *[see Clinical Pharmacology (12.2)]*. The effects of Calcipotriene and Betamethasone Dipropionate Ointment on the HPA axis following treatment durations of longer than 4 weeks have not been adequately studied.

If HPA axis suppression is documented, gradually withdraw the drug, reduce the frequency of application, or substitute with a less potent corticosteroid.

Cushing's syndrome and hyperglycemia may also occur due to the systemic effects of topical corticosteroids. These complications are rare and generally occur after prolonged exposure to excessively large doses, especially of high-potency topical corticosteroids.

Pediatric patients may be more susceptible to systemic toxicity due to their higher skin surface to body mass ratios *[see Use in Specific Populations (8.4), Clinical Pharmacology (12.2)]*.

Use of more than one corticosteroid-containing product at the same time may increase the total systemic corticosteroid exposure.

5.3 Ophthalmic Adverse Reactions

Use of topical corticosteroids, including Calcipotriene and Betamethasone Dipropionate Ointment, may increase the risks of glaucoma and posterior subcapsular cataract. Glaucoma and cataracts have been reported in postmarketing experience with the use of topical corticosteroid products, including topical clobetasol products.

Avoid contact of Calcipotriene and Betamethasone Dipropionate Ointment with eyes. Advise patients to report any visual symptoms and consider referral to an ophthalmologist for evaluation.

5.4 Allergic Contact Dermatitis with Topical Corticosteroids

Allergic contact dermatitis to any component of topical corticosteroids is usually diagnosed by a failure to heal rather than a clinical exacerbation. Clinical diagnosis of allergic contact dermatitis can be confirmed by patch testing.

5.5 Allergic Contact Dermatitis with Topical Calcipotriene

Allergic contact dermatitis has been observed with use of topical calcipotriene. Clinical diagnosis of allergic contact dermatitis can be confirmed by patch testing.

5.6 Skin Irritation

If irritation develops, treatment with Calcipotriene and Betamethasone Dipropionate Ointment should be discontinued and appropriate therapy instituted.

5.7 Risk of Ultraviolet Light Exposure

Patients who apply Calcipotriene and Betamethasone Dipropionate Ointment to exposed skin should avoid excessive exposure to either natural or artificial sunlight, including tanning booths, sun lamps, etc. Physicians may wish to limit or avoid use of phototherapy in patients who use Calcipotriene and Betamethasone Dipropionate Ointment.

6 ADVERSE REACTIONS

Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in practice.

6.1 Clinical Trials Experience

Clinical Trials Conducted in Subjects 18 years and older with Plaque Psoriasis

The data described below reflect exposure to Calcipotriene and Betamethasone Dipropionate Ointment in 2448 subjects with plaque psoriasis, including 1992 exposed for 4 weeks, and 289 exposed for 8 weeks.

Calcipotriene and Betamethasone Dipropionate Ointment was studied primarily in placebo- and active-controlled trials (N = 1176, and N = 1272, respectively). The population was 15-97 years old, 61% males and 39% females, mostly white (97%) and had a baseline disease severity ranging from mild to very severe. Most subjects received once daily application, and the median weekly dose was 24.5 g.

The percentage of subjects reporting at least one adverse event was 27.1% in the Calcipotriene and Betamethasone Dipropionate Ointment group, 33.0% in the calcipotriene group, 28.3% in the betamethasone group, and 33.4% in the vehicle group.

Table 1 Adverse Events Reported by ≥1% of Subjects by Preferred Term

	Calcipotriene and			

	Betamethasone Dipropionate Ointment N = 2448	Calcipotriene N = 3197	Betamethasone dipropionate N = 1164	Vehicle N = 470
Any Adverse Event	663 (27.1)	1055 (33.0)	329 (28.3)	157 (33.4)
Preferred Term	**# of subjects (%)**			
Pruritus	75 (3.1)	183 (5.7)	38 (3.3)	43 (9.1)
Headache	69 (2.8)	75 (2.3)	44 (3.8)	12 (2.6)
Nasopharyngitis	56 (2.3)	77 (2.4)	34 (2.9)	9 (1.9)
Psoriasis	30 (1.2)	47 (1.5)	14 (1.2)	5 (1.1)
Rash scaly	30 (1.2)	40 (1.3)	0 (0.0)	1 (0.2)
Influenza	23 (0.9)	34 (1.1)	14 (1.2)	6 (1.3)
Upper respiratory tract infection	20 (0.8)	19 (0.6)	12 (1.0)	3 (0.6)
Erythema	15 (0.6)	54 (1.7)	3 (0.3)	5 (1.1)
Application site pruritus	13 (0.5)	24 (0.8)	10 (0.9)	6 (1.3)
Skin irritation	11 (0.4)	60 (1.9)	8 (0.7)	5 (1.1)
Pain	7 (0.3)	12 (0.4)	3 (0.3)	5 (1.1)
Burning sensation	6 (0.2)	30 (0.9)	3 (0.3)	6 (1.3)

A lesional/perilesional adverse event was generally defined as an adverse event located ≤ 2 cm from the lesional border.

Table 2 Lesional/Perilesional Adverse Events Reported by ≥1% of Subjects

	Calcipotriene and Betamethasone Dipropionate Ointment N = 2448	Calcipotriene N = 3197	Betamethasone dipropionate N = 1164	Vehicle N = 470
Any Adverse Event	213 (8.7)	419 (13.1)	85 (7.3)	76 (16.2)
Preferred Term	**# of subjects (%)**			
Pruritus	69 (2.8)	170 (5.3)	31 (2.7)	41 (8.7)
Rash scaly	29 (1.2)	38 (1.2)	0 (0.0)	0 (0.0)
Application site pruritus	12 (0.5)	24 (0.8)	10 (0.9)	6 (1.3)
Erythema	9 (0.4)	36 (1.1)	2 (0.2)	4 (0.9)
Skin irritation	9 (0.4)	51 (1.6)	8 (0.7)	5 (1.1)
Burning sensation	6 (0.2)	25 (0.8)	3 (0.3)	5 (1.1)

For subjects who reported lesional/perilesional adverse events, the median time to onset was 7 days for Calcipotriene and Betamethasone Dipropionate Ointment, 7 days for calcipotriene, 5 days for betamethasone dipropionate, and 3 days for vehicle.

Other less common reactions (less than 1% but more than 0.1%) were, in decreasing order of incidence, folliculitis, rash papular, rash pustular, and skin hypopigmentation. Skin atrophy, telangiectasia and skin hyperpigmentation were reported infrequently (0.1%).

In a separate trial, subjects (N = 207) with at least moderate disease severity were given Calcipotriene and Betamethasone Dipropionate Ointment intermittently on an "as needed" basis for up to 52 weeks. The median use was 15.4 g per week. The effects of Calcipotriene and Betamethasone Dipropionate Ointment on calcium metabolism were not studied and the effects on the HPA axis were not adequately studied. The following adverse reactions were reported by 1% or more of the subjects: pruritus (7.2%), psoriasis (3.4%), skin atrophy (1.9%), folliculitis (1.4%), burning sensation (1.4%), skin depigmentation (1.4%), ecchymosis (1.0%), erythema (1.0%) and hand dermatitis (1.0%). One case of serious flare-up of psoriasis was reported.

6.2 Postmarketing Experience

The following adverse reactions associated with the use of Calcipotriene and Betamethasone Dipropionate Ointment have been identified post-approval: pustular psoriasis and rebound effect.

Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure.

Postmarketing reports for local adverse reactions to topical corticosteroids may also include: striae, dryness, acneiform eruptions, perioral dermatitis, secondary infection and miliaria.

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Risk Summary

Calcipotriene and Betamethasone Dipropionate Ointment contains calcipotriene and betamethasone dipropionate. The limited data with Calcipotriene and Betamethasone Dipropionate Ointment and calcipotriene use in pregnant women are not sufficient to evaluate a Calcipotriene and Betamethasone Dipropionate Ointment-associated or calcipotriene-associated risk for major birth defects, miscarriages, or adverse maternal or fetal outcomes.

Observational studies suggest an increased risk of having low birthweight infants with the maternal use of potent or very potent topical corticosteroids *(see Data)*. Advise pregnant women that Calcipotriene and Betamethasone Dipropionate Ointment may increase the potential risk of having a low birth weight infant and to use Calcipotriene and Betamethasone Dipropionate Ointment on the smallest area of skin and for the shortest duration possible.

In animal reproduction studies, oral administration of calcipotriene to pregnant rats during the period of organogenesis resulted in an increased incidence of minor skeletal abnormalities, including enlarged fontanelles and extra ribs *(see Data)*. Oral administration of calcipotriene to pregnant rabbits during the period of organogenesis had no apparent effects on embryo-fetal development. Subcutaneous administration of betamethasone dipropionate to pregnant rats and rabbits during the period of organogenesis resulted in fetal toxicity, including fetal deaths, reduced fetal weight, and fetal malformations (cleft palate and crooked or short tail) *(see Data)*. The available data do not allow the calculation of relevant comparisons between the systemic exposures of calcipotriene and betamethasone diproprionate observed in animal studies to the systemic exposures that would be expected in humans after topical use of Calcipotriene and Betamethasone Dipropionate Ointment.

The estimated background risk of major birth defects and miscarriage of the indicated population is unknown. In the U.S. general population, the estimated background risk of major birth defects and miscarriage in clinically recognized pregnancies is 2% to 4% and 15% to 20%, respectively.

Data

Human Data

Available observational studies in pregnant women did not identify a drug-associated risk of major birth defects, preterm delivery, or fetal mortality with the use of topical corticosteroids of any potency.

However, when the dispensed amount of potent or very potent topical corticosteroids exceeded 300 g during the entire pregnancy, maternal use was associated with an increased risk of low birth weight in infants.

Animal Data

Embryo-fetal development studies with calcipotriene were performed by the oral route in rats and rabbits. Pregnant rats received dosages of 0, 6, 18, or 54 mcg/kg/day (0, 36, 108, and 324 mcg/m^2/day, respectively) on days 6-15 of gestation (the period of organogenesis). There were no apparent effects on maternal survival, behavior, or body weight gain, no effects on litter parameters, and no effects on the incidence of major malformations in fetuses. Fetuses from dams dosed at 54 mcg/kg/day exhibited a significantly increased incidence of minor skeletal abnormalities, including enlarged fontanelles and extra ribs.

Pregnant rabbits were dosed daily with calcipotriene at exposures of 0, 4, 12, or 36 mcg/kg/day (0, 48, 144, and 432 mcg/m^2/day, respectively) on days 6-18 of gestation (the period of organogenesis). Mean maternal body weight gain was reduced in animals dosed at 12 or 36 mcg/kg/day. The incidence of fetal deaths was increased in the group dosed at 36 mcg/kg/day; reduced fetal weight was also observed in this group. The incidence of major malformations among fetuses was not affected. An increase in the incidence of minor skeletal abnormalities, including incomplete ossification of sternebrae, pubic bones, and forelimb phalanges, was observed in the group dosed at 36 mcg/kg/day.

Embryo-fetal development studies with betamethasone dipropionate were performed via subcutaneous injection in mice and rabbits. Pregnant mice were administered doses of 0, 156, 625, or 2500 mcg/kg/day (0, 468, 1875, and 7500 mcg/m^2/day, respectively) on days 7 through 13 of gestation (the period of organogenesis). Betamethasone dipropionate induced fetal toxicity, including fetal deaths, reduced fetal weight, malformations (increased incidence of the cleft palate and crooked or short tail), and minor skeletal abnormalities (delayed ossification of vertebra and sternebrae). Fetal toxicity was observed at the lowest exposure that was evaluated (156 mcg/kg/day).

Pregnant rabbits were injected subcutaneously at dosages of 0, 0.625, 2.5, and 10 mcg/kg/day (0, 7.5, 30, and 120 mcg/m^2/day, respectively) on days 6 through 18 of gestation (the period of organogenesis). Betamethasone dipropionate induced fetal toxicity, including fetal deaths, reduced fetal weight, external malformations (including malformed ears, cleft palate, umbilical hernia, kinked tail, club foot, and club hand), and skeletal malformations (including absence of phalanges of the first digit and cranial dysplasia) at dosages of 2.5 mcg/kg/day and above.

Calcipotriene was evaluated for effects on peri- and post-natal development when orally administered to pregnant rats at dosages of 0, 6, 18 or 54 mcg/kg/day (0, 36, 108, and 324 mcg/m^2/day, respectively) from gestation day 15 through day 20 postpartum. No remarkable effects were observed on any parameter, including survival, behavior, body weight, litter parameters, or the ability to nurse or rear pups.

Betamethasone dipropionate was evaluated for effects on peri- and post-natal development when orally administered to pregnant rats at dosages of 0, 100, 300, and 1000 mcg/kg/day (0, 600, 1800, and 6000 mcg/m^2/day, respectively) from gestation day 6 through day 20 postpartum. Mean maternal body weight was significantly reduced on gestation day 20 in animals dosed at 300 and 1000 mcg/kg/day. The mean duration of gestation was slightly, but statistically significantly, increased at 100, 300, and 1000 mcg/kg/day. The mean percentage of pups that survived to day 4 was reduced in relation to dosage. On lactation day 5, the percentage of pups with a reflex to right themselves when placed on their back was significantly reduced at 1000 mcg/ kg/day. No effects on the ability of pups to learn were observed, and the ability of the offspring of treated rats to reproduce was not affected.

8.2 Lactation

Risk Summary

There is no information regarding the presence of topically administered calcipotriene and

betamethasone dipropionate in human milk, the effects on the breastfed infant, or the effects on milk production. It is not known whether topically administered calcipotriene or corticosteroids could result in sufficient systemic absorption to produce detectable quantities in human milk. The developmental and health benefits of breastfeeding should be considered along with the mother's clinical need for Calcipotriene and Betamethasone Dipropionate Ointment and any potential adverse effects on the breastfed child from Calcipotriene and Betamethasone Dipropionate Ointment or from the underlying maternal condition.

Clinical Considerations

To minimize potential exposure to the breastfed infant via breast milk, use Calcipotriene and Betamethasone Dipropionate Ointment on the smallest area of skin and for the shortest duration possible while breastfeeding. Advise breastfeeding women not to apply Calcipotriene and Betamethasone Dipropionate Ointment directly to the nipple and areola to avoid direct infant exposure *[see Use in Specific Populations (8.4)]*.

8.4 Pediatric Use

Safety and effectiveness of the use of Calcipotriene and Betamethasone Dipropionate Ointment in pediatric patients under the age of 12 years have not been established.

The safety and effectiveness of Calcipotriene and Betamethasone Dipropionate Ointment for the treatment of plaque psoriasis have been established in the age group 12 to 17 years. In a prospective, uncontrolled trial, 33 pediatric subjects ages 12-17 years with plaque psoriasis on the body were treated with Calcipotriene and Betamethasone Dipropionate Ointment for 4 weeks up to a maximum of 55.8 g per week. Subjects were assessed for HPA axis suppression and effects on calcium metabolism. No adverse effects on adrenal suppression were observed. No hypercalcemia was observed but one subject had a possible treatment-related increase in urinary calcium *[see Clinical Pharmacology (12.2)]*.

Because of a higher ratio of skin surface area to body mass, pediatric patients are at a greater risk than adults of systemic toxicity when treated with topical drugs. They are, therefore, also at greater risk of HPA axis suppression and adrenal insufficiency upon the use of topical corticosteroids *[see Warnings and Precautions (5.2)]*.

Rare systemic toxicities such as Cushing's syndrome, linear growth retardation, delayed weight gain, and intracranial hypertension have been reported in pediatric patients, especially those with prolonged exposure to large doses of high potency topical corticosteroids.

Local adverse reactions including striae have also been reported with use of topical corticosteroids in pediatric patients.

8.5 Geriatric Use

Of the total number of subjects in the clinical studies of Calcipotriene and Betamethasone Dipropionate Ointment, approximately 14% were 65 years and older and approximately 3% were 75 years and over.

No overall differences in safety or effectiveness of Calcipotriene and Betamethasone Dipropionate Ointment were observed between these subjects and younger subjects. All other reported clinical experience has not identified any differences in response between elderly and younger patients. However, greater sensitivity of some older individuals cannot be ruled out.

10 OVERDOSAGE

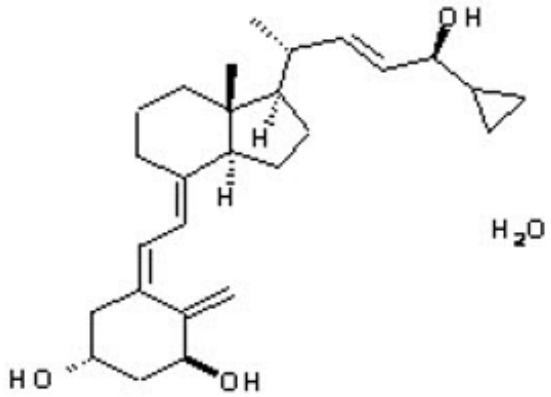
Topically applied Calcipotriene and Betamethasone Dipropionate Ointment can be absorbed in sufficient amounts to produce systemic effects *[see Warnings and Precautions (5.1, 5.2)]*.

11 DESCRIPTION

Calcipotriene and Betamethasone Dipropionate Ointment, 0.005%/0.064% contains calcipotriene hydrate and betamethasone dipropionate. It is intended for topical use only.

Calcipotriene hydrate is a synthetic vitamin D_3 analogue.

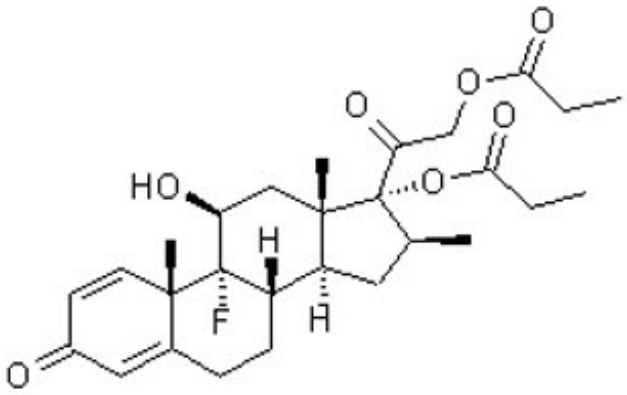
Chemically, calcipotriene hydrate is (5Z,7E,22E,24S)-24-cyclopropyl-9,10-secochola-5,7,10(19),22-tetraene-1(alpha),3(beta),24-triol,hydrate, with the empirical formula $C_{27}H_{40}O_3,H_2O$, a molecular weight of 430.6, and the following structural formula:



Calcipotriene hydrate is a white to almost white crystalline compound.

Betamethasone dipropionate is a synthetic corticosteroid.

Betamethasone dipropionate has the chemical name 9-fluoro-11(beta), 17,21-trihydroxy-16(beta)-methylpregna-1,4-diene-3,20-dione17,21-dipropionate, with the empirical formula $C_{28}H_{37}FO_7$, a molecular weight of 504.6, and the following structural formula:



Betamethasone dipropionate is a white to almost white odorless powder.

Each gram of Calcipotriene and Betamethasone Dipropionate Ointment contains 52.18 mcg of calcipotriene hydrate (equivalent to 50 mcg of calcipotriene) and 0.643 mg of betamethasone dipropionate (equivalent to 0.5 mg of betamethasone) in an off-white to yellow paraffin ointment base of butylhydroxytoluene, mineral oil, polyoxypropylene stearyl ether, all-rac-alpha-tocopherol, and white petrolatum.

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

Calcipotriene and Betamethasone Dipropionate Ointment combines the pharmacological effects of calcipotriene hydrate as a synthetic vitamin D_3 analogue and betamethasone dipropionate as a synthetic corticosteroid. However, while their pharmacologic and clinical effects are known, the exact mechanisms of their actions in plaque psoriasis are unknown.

12.2 Pharmacodynamics

Vasoconstriction:

In a vasoconstrictor trial in healthy subjects, the skin blanching response of Calcipotriene and Betamethasone Dipropionate Ointment was consistent with that of a potent corticosteroid when compared with other topical corticosteroids. However, similar blanching scores do not necessarily imply therapeutic equivalence.

Hypothalamic-Pituitary-Adrenal (HPA) Axis Suppression:

HPA axis suppression was evaluated in four trials (Trial A, B, C and D) following the application of Calcipotriene and Betamethasone Dipropionate Ointment.

In Trial A, Calcipotriene and Betamethasone Dipropionate Ointment was applied once daily for 4 weeks to adult subjects (N = 12) with plaque psoriasis to study its effects on the hypothalamic-pituitary-adrenal (HPA) axis. Of eleven subjects tested, none demonstrated adrenal suppression as indicated by a 30-minute post-stimulation cortisol level ≤ 18 mcg/dL.

In Trial B, Calcipotriene and Betamethasone Dipropionate Ointment was evaluated in adult subjects with plaque psoriasis (N = 19). One subject demonstrated adrenal suppression.

In Trial C, HPA axis suppression was evaluated in adult subjects (N=32) with extensive plaque psoriasis involving at least 30% of the scalp and, in total, 15-30% of the body surface area. Treatment consisted of once daily application of Taclonex Scalp® Topical Suspension on the scalp in combination with Calcipotriene and Betamethasone Dipropionate Ointment on the body. Adrenal suppression as indicated by a 30-minutes post-stimulation cortisol level < 18 mcg/dL was observed in 5 of 32 subjects (15.6%) after 4 weeks of treatment as per the recommended duration of use *[see Dosage and Administration (2)]*.

In Trial D, HPA axis suppression was evaluated in subjects 12 to 17 years (N=32) with plaque psoriasis of the body involving 5-30% of the body surface area. Treatment consisted of once daily application of Calcipotriene and Betamethasone Dipropionate Ointment to the affected areas for up to 4 weeks. Mean weekly dose was 29.6 g with a range of 8.1-55.8 g/week. Adrenal suppression as indicated by a 30-minute post-stimulation cortisol level ≤18 mcg/dL was observed in none of 32 evaluable subjects after 4 weeks of treatment *[see Use in Specific Populations (8.4)]*.

Effects on Calcium Metabolism

In Trial C described above, the effects of once daily application of Calcipotriene and Betamethasone Dipropionate Ointment on the body in combination with Taclonex Scalp® Topical Suspension on the scalp on calcium metabolism were also examined. Elevated urinary calcium levels outside the normal range were observed in 1 of 35 subjects (2.9%) after 4 weeks of treatment.

In Trial D described above, calcium metabolism was evaluated in a total of 33 subjects aged 12 to 17 years with plaque psoriasis involving 5-30% of the body surface area who underwent once daily application of Calcipotriene and Betamethasone Dipropionate Ointment for up to 4 weeks. No cases of hypercalcemia and no clinically relevant changes in urinary calcium were reported. However, one subject had a normal urinary calcium:creatinine ratio at baseline (3.75 mmol/g), which increased above the normal range at week 4 (16 mmol/g). There were no relevant changes in albumin-corrected serum calcium or other markers of calcium metabolism for this subject. The clinical significance of this finding is unknown.

12.3 Pharmacokinetics

Absorption

In Trial C described above, the systemic effect of Calcipotriene and Betamethasone Dipropionate Ointment in extensive plaque psoriasis was investigated. In this trial, the serum levels of calcipotriene

and betamethasone dipropionate and their major metabolites were measured after 4 weeks (maximum recommended duration of treatment) and also after 8 weeks of once daily application of Calcipotriene and Betamethasone Dipropionate Ointment on the body in combination with Taclonex Scalp® Topical Suspension on the scalp. Both calcipotriene and betamethasone dipropionate were below the lower limit of quantification in all serum samples of the 34 subjects evaluated. However, one major metabolite of calcipotriene (MC1080) was quantifiable in 10 of 34 (29.4%) subjects at week 4 and in five of 12 (41.7%) subjects at week 8. The major metabolite of betamethasone dipropionate, betamethasone 17-propionate (B17P) was also quantifiable in 19 of 34 (55.9%) subjects at week 4 and seven of 12 (58.3%) subjects at week 8. The serum concentrations for MC1080 ranged from 20-75 pg/mL. The clinical significance of this finding is unknown.

Metabolism

Calcipotriene:

Calcipotriene metabolism following systemic uptake is rapid and occurs in the liver. The primary metabolites of calcipotriene are less potent than the parent compound.

Calcipotriene is metabolized to MC1046 (the alpha,beta-unsaturated ketone analogue of calcipotriene), which is metabolized further to MC1080 (a saturated ketone analogue). MC1080 is the major metabolite in plasma. MC1080 is slowly metabolized to calcitroic acid.

Betamethasone dipropionate:

Betamethasone dipropionate is metabolized to betamethasone 17-propionate and betamethasone, including the 6beta-hydroxy derivatives of those compounds by hydrolysis. Betamethasone 17-propionate (B17P) is the primary metabolite.

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

When calcipotriene was applied topically to mice for up to 24 months at dosages of 3, 10 and 30 mcg/kg/day (9, 30 and 90 mcg/m^2/day, respectively), no significant changes in tumor incidence were observed when compared to control.

A 104-week oral carcinogenicity study was conducted with calcipotriene in male and female rats at doses of 1, 5 and 15 mcg/kg/day (6, 30, and 90 mcg/m^2/day, respectively). Beginning week 71, the dosage for high-dose animals of both genders was reduced to 10 mcg/kg/day (60 mcg/m^2/day). A treatment-related increase in benign C-cell adenomas was observed in the thyroid of females that received 15 mcg/kg/day. A treatment-related increase in benign pheochromocytomas was observed in the adrenal glands of males that received 15 mcg/kg/day. No other statistically significant differences in tumor incidence were observed when compared to control. The relevance of these findings to patients is unknown.

When betamethasone dipropionate was applied topically to CD-1 mice for up to 24 months at dosages approximating 1.3, 4.2 and 8.5 mcg/kg/day in females, and 1.3, 4.2, and 12.9 mcg/kg/day in males (up to 26 mcg/m^2/day and 39 mcg/m^2/day, in females and males, respectively), no significant changes in tumor incidence were observed when compared to control.

When betamethasone dipropionate was administered via oral gavage to male and female Sprague Dawley rats for up to 24 months at dosages of 20, 60, and 200 mcg/kg/day (120, 360, and 1200 mcg/m^2/day, respectively), no significant changes in tumor incidence were observed when compared to control.

Calcipotriene did not elicit any genotoxic effects in the Ames mutagenicity assay, the mouse lymphoma TK locus assay, the human lymphocyte chromosome aberration test, or the mouse micronucleus test. Betamethasone dipropionate did not elicit any genotoxic effects in the Ames mutagenicity assay, the mouse lymphoma TK locus assay, or in the rat micronucleus test.

Studies in rats with oral doses of up to 54 mcg/kg/day (324 mcg/m^2/day) of calcipotriene indicated no impairment of fertility or general reproductive performance. Studies in male rats at oral doses of up to 200 mcg/kg/day (1200 mcg/m^2/day), and in female rats at oral doses of up to 1000 mcg/kg/day (6000 mcg/m^2/day), of betamethasone dipropionate indicated no impairment of fertility.

14 CLINICAL STUDIES

Clinical Trials Conducted in Subjects 18 years and older with Plaque Psoriasis

In an international, multi-center, double-blind, vehicle- and active-controlled, parallel-group trial, 1603 subjects with mild to very severe plaque psoriasis on trunk and limbs were treated once daily for 4 weeks. Subjects were randomized to one of four treatment arms: Calcipotriene and Betamethasone Dipropionate Ointment, calcipotriene hydrate 50 mcg/g in the same vehicle, betamethasone dipropionate 0.64 mg/g in the same vehicle, and vehicle alone. The mean age of the subjects was 48.4 years and 60.5% were male. Most subjects had disease of moderate severity at baseline.

Efficacy was assessed as the proportion of subjects with absent or very mild disease according to the Investigator's Global Assessment of Disease Severity at end of treatment (4 weeks). "Absent" disease was defined as no evidence of redness, thickness, or scaling. "Very mild disease" was defined as controlled disease, but not entirely cleared: lesions with some discoloration with absolutely minimal thickness, i.e. the edges to the lesion(s) could just be felt. Table 3 contains the response rates for this trial.

Table 3 Percentage of Subjects with Absent or Very Mild Disease According to the Investigator's Global Assessment of Disease Severity at End of Treatment (4 weeks)*

	Calcipotriene and Betamethasone Dipropionate Ointment N = 490	**Calcipotriene N = 480**	**Betamethasone dipropionate N = 476**	**Vehicle N = 157**
Absent or very mild disease	48.0%	16.5%	26.3%	7.6%

* Subjects with mild disease at baseline were required to have "Absent" disease to be considered a success.

In addition to the pivotal trial (N = 490), four randomized, double-blind, vehicle- or active-controlled, parallel-group trials were conducted and provided supportive evidence of efficacy. These trials included a total of 1058 subjects treated with Calcipotriene and Betamethasone Dipropionate Ointment once daily for up to 4 weeks.

Clinical Trial Conducted in Subjects 12 to 17 years with Plaque Psoriasis

A prospective, uncontrolled trial (N=33) was conducted in pediatric subjects ages 12 to 17 years with plaque psoriasis involving 5-30% of the body surface area. Approximately 91% of subjects had moderate disease at baseline. Subjects were treated once daily for up to 4 weeks with Calcipotriene and Betamethasone Dipropionate Ointment. All subjects were evaluated for safety including calcium metabolism (N=33) and 32 subjects were evaluated for HPA axis suppression *[see Clinical Pharmacology (12.2)]*.

16 HOW SUPPLIED/STORAGE AND HANDLING

16.1 How Supplied

Calcipotriene and Betamethasone Dipropionate Ointment is off-white to yellow in color, available in

collapsible tubes of:

60 gram (NDC 66993-938-61)
100 gram (NDC 66993-938-65)

16.2 Storage

Store Calcipotriene and Betamethasone Dipropionate Ointment between 20°C - 25°C (68°F - 77°F); excursions permitted between 15°C - 30°C (59°F - 86°F). [See USP controlled room temperature.]

16.3 Handling

Keep out of reach of children.

17 PATIENT COUNSELING INFORMATION

See FDA-approved patient labeling (Patient Information).

Inform patients of the following:

- Instruct adult patients (18 years and older) not to use more than 100 g per week.
- Instruct pediatric patients (12 to 17 years) not to use more than 60 g per week.
- Discontinue therapy when control is achieved unless directed otherwise by the physician.
- Avoid use of Calcipotriene and Betamethasone Dipropionate Ointment on the face, underarms, groin or eyes. If this medicine gets on face or in eyes, wash area right away.
- Do not occlude the treatment area with a bandage or other covering unless directed by the physician.
- Note that local reactions and skin atrophy are more likely to occur with occlusive use, prolonged use or use of higher potency corticosteroids.
- Wash hands after application.
- Advise patients to report any visual symptoms to their healthcare providers.
- Advise a woman to use Calcipotriene and Betamethasone Dipropionate Ointment on the smallest area of skin and for the shortest duration possible while pregnant or breastfeeding. Advise breastfeeding women not to apply Calcipotriene and Betamethasone Dipropionate Ointment directly to the nipple and areola to avoid direct infant exposure.
- Instruct patients not to use other products containing calcipotriene or a corticosteroid should not be used with Calcipotriene and Betamethasone Dipropionate Ointment without first talking to the physician.
- Instruct patients who use Calcipotriene and Betamethasone Dipropionate Ointment to avoid excessive exposure to either natural or artificial sunlight (including tanning booths, sun lamps, etc.).

Manufactured by:
LEO Laboratories Ltd. (LEO Pharma)
Dublin 12, Ireland

Distributed by:
Prasco Laboratories
Mason, OH 45040 USA

PATIENT INFORMATION
Calcipotriene and Betamethasone Dipropionate Ointment, 0.005%/0.064%

Read the Patient Information that comes with Calcipotriene and Betamethasone Dipropionate Ointment before you start using it and each time you refill your prescription. There may be new information. This leaflet does not take the place of talking with your doctor about your condition or treatment.

Important information: Calcipotriene and Betamethasone Dipropionate Ointment is for use on the skin

only (topical use only). Do not use Calcipotriene and Betamethasone Dipropionate Ointment on the face, under arms or on groin area. Do not swallow Calcipotriene and Betamethasone Dipropionate Ointment. Another product, Calcipotriene and Betamethasone Dipropionate Topical Suspension contains the same medicine that is in Calcipotriene and Betamethasone Dipropionate Ointment and is used to treat plaque psoriasis on the scalp. If you use both medicines to treat your plaque psoriasis, be sure to follow your doctor's directions carefully so that you do not use too much of one or both of these medications.

What is Calcipotriene and Betamethasone Dipropionate Ointment?

Calcipotriene and Betamethasone Dipropionate Ointment is a prescription medicine that is for use on the skin only (a topical medicine). Calcipotriene and Betamethasone Dipropionate Ointment is used to treat plaque psoriasis in patients 12 years of age and older.

Calcipotriene and Betamethasone Dipropionate Ointment has not been studied in patients under the age of 12 years.

Who should not use Calcipotriene and Betamethasone Dipropionate Ointment?

Do not use Calcipotriene and Betamethasone Dipropionate Ointment if you:

- have thin skin (atrophy) at the site to be treated
- are allergic to anything in Calcipotriene and Betamethasone Dipropionate Ointment. See the end of this leaflet for a complete list of ingredients.

What should I tell my doctor before using Calcipotriene and Betamethasone Dipropionate Ointment?

Tell your doctor about all of your health conditions, including if you:

- have a skin infection. Your skin infection should be treated before starting Calcipotriene and Betamethasone Dipropionate Ointment.
- have a calcium metabolism disorder
- have one of the following types of psoriasis:
  - erythrodermic psoriasis
  - exfoliative psoriasis
  - pustular psoriasis
- are getting phototherapy treatments (light therapy) for your psoriasis
- are pregnant or planning to become pregnant. It is not known if Calcipotriene and Betamethasone Dipropionate Ointment can harm your unborn baby. You and your doctor will have to decide if Calcipotriene and Betamethasone Dipropionate Ointment is right for you while pregnant.
- are breastfeeding or plan to breastfeed. It is not known if Calcipotriene and Betamethasone Dipropionate Ointment passes into your milk and if it can harm your baby. If you use Calcipotriene and Betamethasone Dipropionate Ointment while breastfeeding, use Calcipotriene and Betamethasone Dipropionate Ointment on the smallest area of skin and for the shortest time needed. If you use Calcipotriene and Betamethasone Dipropionate Ointment, do not apply Calcipotriene and Betamethasone Dipropionate Ointment to your nipple or areola to avoid getting Calcipotriene and Betamethasone Dipropionate Ointment into your baby's mouth.

Tell your doctor about all the medicines you take, including prescription, and nonprescription medicines, vitamins and herbal supplements.

Calcipotriene and Betamethasone Dipropionate Ointment and some other medicines can interact with each other. Especially tell your doctor if you use:

- other corticosteroid medicines
- other medicines for your psoriasis

How should I use Calcipotriene and Betamethasone Dipropionate Ointment?

- Use Calcipotriene and Betamethasone Dipropionate Ointment exactly as prescribed by your doctor.

- If you are 18 years of age or older, you should not use more than 100 grams of Calcipotriene and Betamethasone Dipropionate Ointment in 1 week.
- If you are 12 to 17 years of age, you should not use more than 60 grams of Calcipotriene and Betamethasone Dipropionate Ointment in 1 week.
- Apply Calcipotriene and Betamethasone Dipropionate Ointment once a day to the areas of your skin affected by psoriasis. Gently rub Calcipotriene and Betamethasone Dipropionate Ointment into your affected skin areas.
- Only use Calcipotriene and Betamethasone Dipropionate Ointment as directed by your doctor. Calcipotriene and Betamethasone Dipropionate Ointment is recommended for up to 4 weeks of treatment. Do not use Calcipotriene and Betamethasone Dipropionate Ointment for more than 4 weeks unless prescribed by your doctor.
- Do not use Calcipotriene and Betamethasone Dipropionate Ointment on the face, under arms or on groin area. If you accidentally get Calcipotriene and Betamethasone Dipropionate Ointment on the face or in the eyes wash the area with water right away.
- If you forget to use Calcipotriene and Betamethasone Dipropionate Ointment, use it as soon as you remember. Then go on as before.
- Wash your hands well after applying Calcipotriene and Betamethasone Dipropionate Ointment.
- If you are breastfeeding, do not use Calcipotriene and Betamethasone Dipropionate Ointment on the breast while nursing.

Using Calcipotriene and Betamethasone Dipropionate Ointment:

Do not bandage or tightly cover the treated skin area.

Remove the cap and check that the aluminum seal covers the tube before the first use. To break the seal, turn the cap over and punch through the seal.

What should I avoid while using Calcipotriene and Betamethasone Dipropionate Ointment?

Avoid spending a long time in the sunlight. Avoid tanning booths and sunlamps. Use sunscreen if you have to be in the sunlight. Talk to your doctor if you get a sunburn.

What are the possible side effects of Calcipotriene and Betamethasone Dipropionate Ointment?

The most common side effects are:
- itching
- rash

Other less common side effects with Calcipotriene and Betamethasone Dipropionate Ointment include:
- redness of the skin
- skin irritation
- skin burning
- inflamed hair pores (folliculitis)
- change of skin color (at the site of application)
- rash with pus-filled papules
- thinning of the skin (atrophy)
- swollen fine blood vessels (this makes your skin appear red at the site of application)

Calcipotriene and Betamethasone Dipropionate Ointment may cause serious side effects. Serious side effects are more likely to happen if you use too much Calcipotriene and Betamethasone Dipropionate Ointment, use it for too long, or use it with other topical medicines that contain corticosteroids, calcipotriene, or certain other ingredients. Check with your doctor before using other topical medicines. Calcipotriene and Betamethasone Dipropionate Ointment can pass through your skin. Serious side effects may include:
- too much calcium in your blood or urine

- adrenal gland problems

Your doctor may do special blood and urine tests to check your calcium levels and adrenal gland function while you are using Calcipotriene and Betamethasone Dipropionate Ointment.
Call your doctor about any side effect that bothers you or that does not go away.

These are not all of the side effects with Calcipotriene and Betamethasone Dipropionate Ointment. Ask your doctor or pharmacist for more information.

Vision problems. Calcipotriene and Betamethasone Dipropionate Ointment may increase your chance of developing cataract(s) and glaucoma. Tell your healthcare provider if you develop blurred vision or other vision problems during treatment with Calcipotriene and Betamethasone Dipropionate Ointment.

How should I store Calcipotriene and Betamethasone Dipropionate Ointment?

- Store Calcipotriene and Betamethasone Dipropionate Ointment at room temperature, 68°F - 77°F (20°C - 25°C); Make sure the cap on the tube is tightly closed.
- Calcipotriene and Betamethasone Dipropionate Ointment has an expiration date (exp.) marked on the tube. Do not use the ointment after this date.
- Keep Calcipotriene and Betamethasone Dipropionate Ointment and all medicines out of the reach of children and pets.

General information about Calcipotriene and Betamethasone Dipropionate Ointment

Medicines are sometimes prescribed for conditions that are not mentioned in patient information leaflets. Do not use Calcipotriene and Betamethasone Dipropionate Ointment for a condition for which it was not prescribed. Do not give Calcipotriene and Betamethasone Dipropionate Ointment to other people, even if they have the same symptoms you have. It may harm them.

This leaflet summarizes the most important information about Calcipotriene and Betamethasone Dipropionate Ointment. If you would like more information, talk with your doctor. You can ask your doctor or pharmacist for information about Calcipotriene and Betamethasone Dipropionate Ointment that is written for health professionals.

What are the ingredients in Calcipotriene and Betamethasone Dipropionate Ointment?

Active ingredients: calcipotriene hydrate, betamethasone dipropionate.
Inactive ingredients: butylhydroxytoluene, mineral oil, polyoxypropylene stearyl ether, all-rac-alpha-tocopherol, white petrolatum.

Manufactured by:
LEO Laboratories Ltd. (LEO Pharma)
Dublin 12, Ireland

Distributed by:
Prasco Laboratories
Mason, OH 45040 USA

Revised: 03/2020

PRINCIPAL DISPLAY PANEL - 60 g Tube Carton

NDC 66993-938-61
Rx only

PRASCO

Calcipotriene 0.005% and
Betamethasone Dipropionate 0.064%
Ointment

For Topical Use Only
Net Wt. 60 g

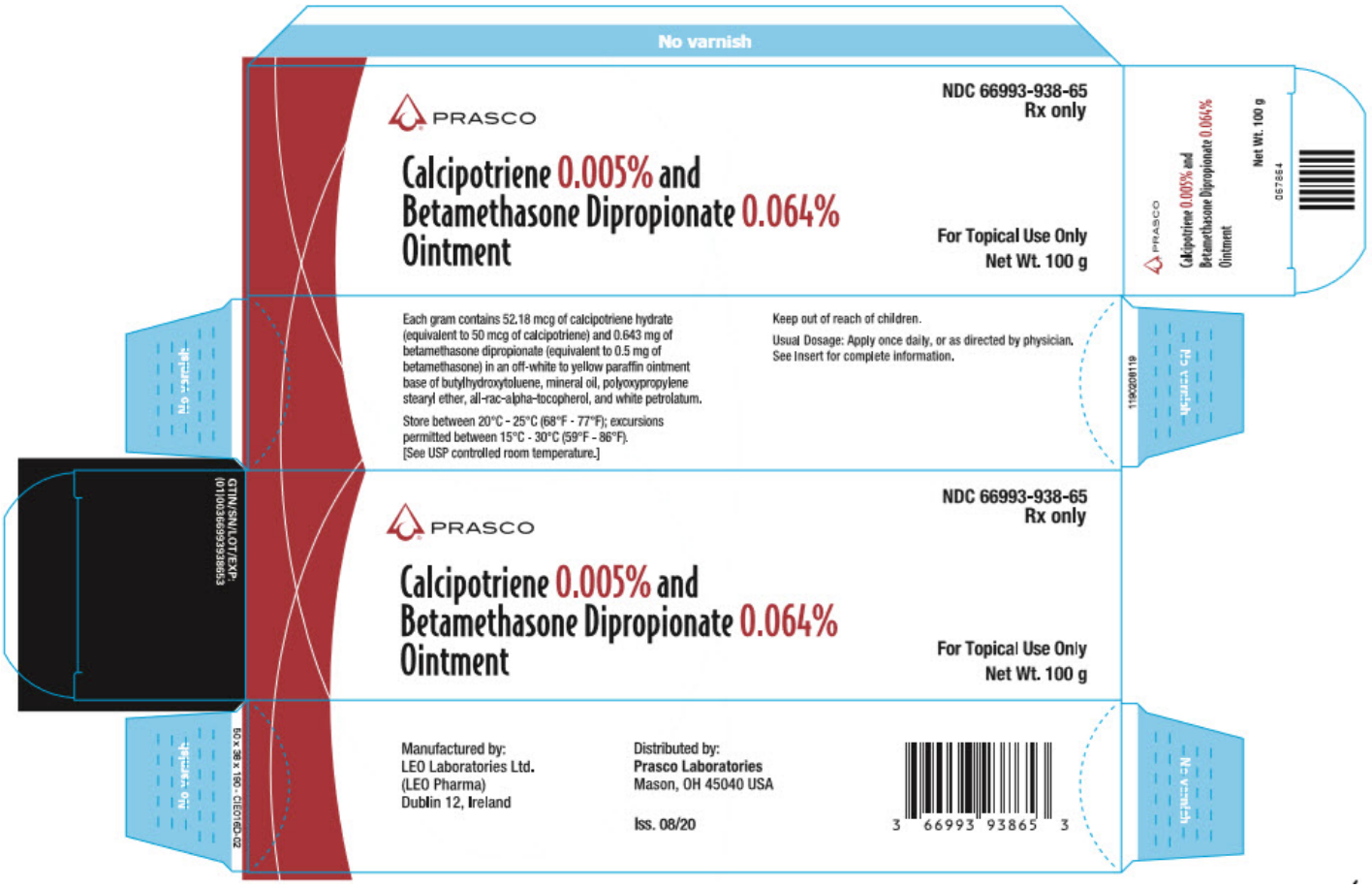
PRINCIPAL DISPLAY PANEL - 100 g Tube Carton

NDC 66993-938-65
Rx only

PRASCO

Calcipotriene 0.005% and
Betamethasone Dipropionate 0.064%
Ointment

For Topical Use Only
Net Wt. 100 g



CALCIPOTRIENE AND BETAMETHASONE DIPROPIONATE

calcipotriene and betamethasone dipropionate ointment

Product Information			
Product Type	HUMAN PRESCRIPTION DRUG	**Item Code (Source)**	NDC:66993-938
Route of Administration	TOPICAL		

Active Ingredient/Active Moiety		
Ingredient Name	**Basis of Strength**	**Strength**
CALCIPOTRIENE HYDRATE (UNII: S7499TYY6G) (CALCIPOTRIENE - UNII:143NQ3779B)	CALCIPOTRIENE	50 ug in 1 g
BETAMETHASONE DIPROPIONATE (UNII: 826Y60901U) (BETAMETHASONE - UNII:9842X06Q6M)	BETAMETHASONE	0.5 mg in 1 g

Inactive Ingredients	
Ingredient Name	**Strength**
.ALPHA.-TOCOPHEROL, DL- (UNII: 7QWA1RIO01)	
MINERAL OIL (UNII: T5L8T28FGP)	
PETROLATUM (UNII: 4T6H12BN9U)	
PPG-11 STEARYL ETHER (UNII: S4G2J0Y0LG)	
BUTYLATED HYDROXYTOLUENE (UNII: 1P9D0Z171K)	

Packaging

#	Item Code	Package Description	Marketing Start Date	Marketing End Date
1	NDC:66993-938-61	1 in 1 CARTON	01/28/2020	
1		60 g in 1 TUBE; Type 0: Not a Combination Product		
2	NDC:66993-938-65	1 in 1 CARTON	01/28/2020	
2		100 g in 1 TUBE; Type 0: Not a Combination Product		

Marketing Information

Marketing Category	Application Number or Monograph Citation	Marketing Start Date	Marketing End Date
NDA AUTHORIZED GENERIC	NDA021852	01/28/2020	

Labeler - Prasco Laboratories (065969375)

Registrant - LEO Pharma Inc. (832692615)

Establishment

Name	Address	ID/FEI	Business Operations
LEO Laboratories Ltd. (LEO Pharma)		219532322	MANUFACTURE(66993-938)

Revised: 8/2020 Prasco Laboratories